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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,129	09/20/2006	Robert Dean Dally	X17115	4638

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EXAMINER	
WILLIS, DOUGLAS M	

ART UNIT	PAPER NUMBER
4161	

NOTIFICATION DATE	DELIVERY MODE
08/20/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@lilly.com

Office Action Summary	Application No.	Applicant(s)	
	10/599,129	DALLY ET AL.	
	Examiner	Art Unit	
	DOUGLAS M. WILLIS	4161	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 8-11* is/are pending in the application.

4a) Of the above claim(s) *10 and 11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,8 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09-20-06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims / Priority

Claims 1, 2 and 8-11 are pending in the current application. According to the *Amendment to the Claims*, filed October 11, 2007, claim 2 was amended and claims 3-7 and 12 were cancelled. This application is a 35 U.S.C. § 371 National Stage Filing of International Application No. PCT/US2005/12191, filed April 08, 2005, which claims priority under 35 U.S.C. § 119(e) to US Provisional Application No. 60/564,538, filed April 22, 2004.

Restrictions / Election of Species

The previous restriction requirement, entered via telephone on July 25, 2008, is hereby amended in-part with this supplemental restriction requirement as follows: the restriction requirement regarding R^1 = (C_3-C_7cycloalkyl)$_{0-1}$(C_1-C_6alkyl) has been withdrawn.

Restriction is required under 35 U.S.C. § 121 and § 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claims 1, 2, 8 and 9, is drawn to substituted pyrrolidines and pharmaceutical compositions of the formula I/I(a)/III, where R^1 = (C_3-C_7cycloalkyl)$_{0-1}$(C_1-C_6alkyl); R^2 = -benzyl; R^3 and R^4, taken together with the carbon to which they are attached, cannot form a C_3-C_6 cycloalkyl ring; R^5 and R^6 taken together cannot form =CHC(O)(C_1-C_4alkoxy); and R^7 and R^8 taken together cannot form a bond.

NOTE: *Claims 1 and 8 are generic to Group I. If Group I is elected, applicant must elect a provisional species,* ***for searching purposes and prosecution on the merits only,*** *clearly identifying a substituted pyrrolidine or pharmaceutical composition of the*

formula I/I(a)/III, including a detailed explanation of how all variables of the formula I/I(a)/III are read upon.

Group II, claims 1, 2, 8 and 9, is drawn to substituted pyrrolidines and pharmaceutical compositions of the formula I/I(a)/III, where R^1 and R^2, as recited, are not as defined above, and R^3 and R^4, taken together with the carbon to which they are attached, cannot form a C_3-C_6 cycloalkyl ring; R^5 and R^6 taken together cannot form =CHC(O)(C_1-C_4alkoxy); and R^7 and R^8 taken together cannot form a bond.

NOTE: *Claims 1 and 8 are generic to Group II. If Group II is elected, applicant must elect a provisional species,* ***for searching purposes and prosecution on the merits only,*** *clearly identifying a substituted pyrrolidine or pharmaceutical composition of the formula I/I(a)/III, including a detailed explanation of how all variables of the formula I/I(a)/III are read upon. Also, further restriction will limit scope to Group II, once defined.*

Group III, claim 10, is drawn to substituted pyrrolidines and pharmaceutical compositions of the formula IV, where R^1 = (C_3-C_7cycloalkyl)$_{0\text{-}1}$(C_1-C_6alkyl); R^2 = -benzyl; R^3 and R^4, taken together with the carbon to which they are attached, cannot form a C_3-C_6 cycloalkyl ring; R^5 and R^6 taken together cannot form =CHC(O)(C_1-C_4alkoxy) or -oxo; and R^7 and R^8 taken together cannot form a bond.

NOTE: *Claims 1 and 8 are generic to Group III. If Group III is elected, applicant must elect a provisional species,* ***for searching purposes and prosecution on the merits only,*** *clearly identifying a substituted pyrrolidine or pharmaceutical composition of the formula IV, including a detailed explanation of how all variables of the formula IV are read upon.*

Group IV, claim 10, is drawn to substituted pyrrolidines and pharmaceutical compositions of the formula IV, where R^1 and R^2, as recited, are not as defined above, and R^3 and R^4, taken together with the carbon to which they are attached, cannot form a C_3-C_6 cycloalkyl ring; R^5 and R^6 taken together cannot form =CHC(O)(C_1-C_4alkoxy) or -oxo; and R^7 and R^8 taken together cannot form a bond.

NOTE: *Claim 10 is generic to Group IV. If Group IV is elected, applicant must elect a provisional species,* ***for searching purposes and prosecution on the merits only,*** *clearly identifying a substituted pyrrolidine or pharmaceutical composition of the formula IV, including a detailed explanation of how all variables of the formula IV are read upon. Also, further restriction will limit scope to Group IV, once defined.*

Group V, claim 11, is drawn to a method for the inhibition of production of A-β peptide, comprising administering… a compound of the formula I/I(a)/III.

NOTE: *Claim 11 is generic to Group V. If Group V is elected, applicant must elect a provisional species,* ***for searching purposes and prosecution on the merits only,*** *clearly identifying a substituted pyrrolidine or pharmaceutical composition of the formula I/I(a)/III, including a detailed explanation of how all variables of the formula I/I(a)/III are read upon. Also, further restriction will limit scope to one of the compound groups listed as Groups I or II above.*

As set forth in Rule 13.1 of the Patent Cooperation Treaty (PCT), "the international application shall relate to one invention only or to a group of inventions." Moreover, as stated in PCT Rule 13.2, the requirement of unity of invention referred to in PCT Rule 13.1 shall be fulfilled "where a group of inventions is claimed in one and the same international application only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features." The expression 'special technical features' shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art, so linked, as to form a single general inventive concept.

The 'special technical feature' among all groups is substituted pyrrolidines and pharmaceutical compositions of the formula I, I(a), III or IV. The inventions listed as Groups I-V do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding 'special technical feature' for the following reasons: WO 04/024081, cited in the international search report, teaches substituted pyrrolidines and pharmaceutical compositions of the formula I, I(a), III or IV, as inhibitors of the beta-secretase enzyme with utility in the treatment of Alzheimer's disease [Abstract; p. 56, lines 24-30]. Consequently, the substituted pyrrolidines and pharmaceutical compositions of the formula I, I(a), III or IV do not share a 'special technical feature' and do not relate to a single general inventive concept under PCT Rule 13.1.

Rejoinder

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. § 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. § 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the

currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Election of Species

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are listed above in *Restrictions*.

The claims are deemed to correspond to the species listed above in the following manner:

Groups I and II - claims 2 and 9; Groups III and IV - claim 10; and Group V - claim 11.

The following claim(s) are generic:

Groups I and II - claims 1 and 8; Groups III and IV - claim 10; and Group V - claim 11.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding 'special technical features' for the following reasons: WO 04/024081, cited in the international search report, teaches substituted pyrrolidines and pharmaceutical compositions of the formula I, I(a), III or IV, as inhibitors of the beta-secretase enzyme with utility in the treatment of Alzheimer's disease [Abstract; p. 56, lines 24-30].

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another

species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. § 101 and/or 35 U.S.C. § 112, first paragraph.

The election of an invention or species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse.

Should applicant traverse on the ground that the inventions or species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions or species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103(a) of the other invention.

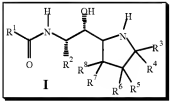
Applicant is required, in reply to this action, to elect a single species, ***for searching purposes and prosecution on the merits only***, to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP §

809.02(a).

Applicant is advised that the reply to this requirement to be complete must include: **(i) an election of a species or invention to be examined even though the requirement may be traversed (37 CFR 1.143)** and **(ii) identification of the claims encompassing the elected invention.**

During a telephone conversation with Mr. Robert Titus on July 25, 2008, a provisional election was made, with traverse, to prosecute the following: a) Group I, claims 1, 2, 8 and 9; and b) substituted pyrrolidine of Formula I/I(a)/III - example 33, p. 160, shown right below, and hereafter referred to as *N*-((1*R*,2*S*)-3-(3,5-difluorophenyl)-1-hydroxy-1-((4*S*)-4-(2-oxo-2-(piperidin-1-yl)ethyl)pyrrolidin-2-yl)propan-2-yl)acetamide hydrochloride, wherein R_1 = -CH_3 (C_3-C_7cycloalkyl)$_{0\text{-}1}$(C_1-C_6alkyl); R^2 = -benzyl; R^3 = -H; R^4 = -H; R^5 = -H; R^6 = -$CH_2C(O)R^{35}$, wherein R^{35} = -$NR^{37}R^{38}$, where R^{37} and R^{38}, taken together with the nitrogen to which they are attached, form a piperidine ring; R^7 = -H; and R^8 = -H. Affirmation of this election must be made by applicant in replying to this Office action.



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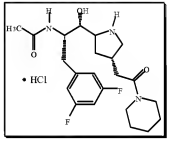
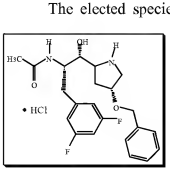


The elected species, shown above, was found to be free of the prior art. Thus, the examiner has expanded the forthcoming prosecution to include all claims relevant to the genus of Group I, and has selected as an alternative species, *N*-((1*R*,2*S*)-1-((4*R*)-4-(benzyloxy)pyrrolidin-2-yl)-3-(3,5-difluorophenyl)-1-hydroxypropan-2-yl)acetamide hydrochloride, shown left, for a first Office action and prosecution on the merits.



Claims 10 and 11 were withdrawn from further consideration, pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Thus, a first Office action on the merits of claims 1, 2, 8 and 9 is contained within.

Claim Rejections - 35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

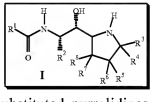
Claims 1, 2, 8 and 9 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for substituted pyrrolidines, hydrochloride salts and pharmaceutical compositions of the formula I/I(a)/III, wherein R^1 = -(C_3-C_7cycloalkyl)$_{0-1}$(C_1-C_6alkyl), -pyridyl, -phenyl or biphenyl, does not reasonably provide enablement for substituted pyrrolidines, hydrochloride salts and pharmaceutical compositions of the formula I/I(a)/III, wherein R^1 = -(C_3-C_7cycloalkyl)$_{0-1}$(C_2-C_6alkenyl), -(C_3-C_7cycloalkyl)$_{0-1}$(C_2-C_6alkynyl), -C_3-C_7cycloalkyl and -H. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention(s) commensurate in scope with these claims. Substituted pyrrolidines, hydrochloride salts and pharmaceutical compositions of the formula I/I(a)/III, wherein R^1 = -(C_3-C_7cycloalkyl)$_{0-1}$(C_2-C_6alkenyl), -(C_3-C_7cycloalkyl)$_{0-1}$(C_2-C_6alkynyl), -C_3-C_7cycloalkyl and -H, as recited in claim 1, have not been adequately enabled in the specification to allow any person having ordinary skill in the art, at the time this invention was made, to make and use substituted pyrrolidines, hydrochloride salts and pharmaceutical compositions of the formula I/I(a)/III, wherein R^1 = -(C_3-

C_7cycloalkyl)$_{0-1}$(C_2-C_6alkenyl), -(C_3-C_7cycloalkyl)$_{0-1}$(C_2-C_6alkynyl), -C_3-C_7cycloalkyl and -H.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is *undue*. These factors include, but are not limited to: (a) breadth of the claims; (b) nature of the invention; (c) state of the prior art; (d) level of one of ordinary skill in the art; (e) level of predictability in the art; (f) amount of direction provided by the inventor; (g) existence of working examples; and (h) quantity of experimentation needed to make or use the invention based on the content of the disclosure. (See *Ex parte Forman* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

The above factors, regarding the present invention, are summarized as follows:

(a) *Breadth of the claims* - the breadth of the claims includes all of the tens of thousands of substituted pyrrolidines, hydrochloride salts and pharmaceutical compositions of the formula I/I(a)/III, shown right;



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(b) *Nature of the invention* - the nature of the evaluation of substituted pyrrolidines, hydrochloride salts and pharmaceutical compositions of the formula I/I(a)/III and the pharmacokinetic behavior of these substances in the human as β-site APP-cleaving enzyme (BACE) inhibitors, useful in the treatment of disorders such as Alzheimer's disease;

(c) *State of the prior art* - *Nature Reviews: Drug Discovery* offers a snapshot of the state of the drug development art. Herein, drug development is stated to follow the widely accepted Ehrlich model which includes: 1) development of a broad synthetic organic chemistry program; 2) subsequent testing of compounds in an appropriate laboratory model for the disease to be treated; and 3) screening of compounds with low toxicity in prospective clinical trials (Jordan, V. C. *Nature Reviews: Drug Discovery,* 2, **2003**, p. 205);

(d) *Level of one of ordinary skill in the art* - the artisans synthesizing applicant's substituted pyrrolidines, hydrochloride salts and pharmaceutical compositions of the formula I/I(a)/III would be a collaborative team of synthetic chemists and/or health practitioners, possessing commensurate degree level and/or skill in the art, as well as several years of professional experience;

(e) *Level of predictability in the art* - Synthetic organic chemistry is quite unpredictable (*In re Marzocchi and Horton* 169 USPQ at 367 ¶ 3). The following excerpt is taken from Dörwald, which has extreme relevance to the synthesis of substituted pyrrolidines, hydrochloride salts and pharmaceutical compositions of the formula I/I(a)/III, wherein R^1 = -(C_3-C_7cycloalkyl)$_{0-1}$(C_2-C_6alkenyl), -(C_3-C_7cycloalkyl)$_{0-1}$(C_2-C_6alkynyl), -C_3-C_7cycloalkyl and -H (Dörwald, F. Zaragoza. *Side Reactions in Organic Synthesis: A Guide to Successful Synthesis Design*, Weinheim: WILEY-VCH Verlag GmbH & Co. KGaA, **2005**, Preface):

Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why.

Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work.

Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious).

(f) *Amount of direction provided by the inventor* - the application is negligent regarding direction with respect to making and using substituted pyrrolidines, hydrochloride salts and pharmaceutical compositions of the formula I/I(a)/III, wherein R^1 = -(C_3-C_7cycloalkyl)$_{0-1}$(C_2-C_6alkenyl), -(C_3-C_7cycloalkyl)$_{0-1}$(C_2-C_6alkynyl), -C_3-C_7cycloalkyl and -H;

(g) *Existence of working examples* - applicant has provided sufficient guidance to make and use substituted pyrrolidines, hydrochloride salts and pharmaceutical compositions of the formula I/I(a)/III, wherein R^1 = -(C_3-C_7cycloalkyl)$_{0-1}$(C_1-C_6alkyl), -pyridyl, -phenyl or biphenyl; however, the disclosure is insufficient to allow extrapolation of the limited examples to enable the scope of the tens of thousands of substituted pyrrolidines, hydrochloride salts and pharmaceutical compositions of the formula I/I(a)/III, wherein R^1 = -(C_3-C_7cycloalkyl)$_{0-1}$(C_2-C_6alkenyl), -(C_3-C_7cycloalkyl)$_{0-1}$(C_2-C_6alkynyl), -C_3-C_7cycloalkyl and -H. The specification lacks working examples of substituted pyrrolidines, hydrochloride salts

and pharmaceutical compositions of the formula I/I(a)/III, wherein R^1 = -(C_3-C_7cycloalkyl)$_{0-1}$(C_2-C_6alkenyl), -(C_3-C_7cycloalkyl)$_{0-1}$(C_2-C_6alkynyl), -C_3-C_7cycloalkyl and -H.

Within the specification, "specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. *Markush* claims must be provided with support in the disclosure for each member of the *Markush* group. Where the constitution and formula of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula." See MPEP § 608.01(p).

(h) *Quantity of experimentation needed to make or use the invention based on the content of the disclosure* - predicting whether a recited compound is in fact one that produces a desired physiological effect at a therapeutic concentration and with useful kinetics, is filled with experimental uncertainty, and without proper guidance, would involve a substantial amount of experimentation (Jordan, V. C. *Nature Reviews: Drug Discovery,* 2, **2003**, pp. 205-213).

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. {*In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)}.

The determination that *undue experimentation* would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. (*In re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404). These factual considerations are discussed comprehensively in MPEP § 2164.08 (scope or breadth of the claims), § 2164.05(a) (nature of the invention and state of the prior art), § 2164.05(b) (level of one of ordinary skill), § 2164.03 (level of predictability in the art and amount of direction provided by the inventor), § 2164.02 (the existence of working examples) and § 2164.06 (quantity of experimentation needed to make or use the invention based

on the content of the disclosure).

Based on a preponderance of the evidence presented herein, the conclusion that applicant is insufficiently enabled for making and using substituted pyrrolidines, hydrochloride salts and pharmaceutical compositions of the formula I/I(a)/III, wherein R^1 = -(C_3-C_7cycloalkyl)$_{0-1}$(C_2-C_6alkenyl), -(C_3-C_7cycloalkyl)$_{0-1}$(C_2-C_6alkynyl), -C_3-C_7cycloalkyl and -H, is clearly justified.

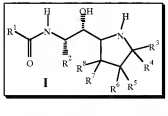
Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 8 and 9 are rejected under 35 U.S.C. § 102(e) as being anticipated by Cumming, et al. in WO 05/016876.

The instant application, recites in claims 1, 2, 8 and 9, substituted pyrrolidines, hydrochloride salts and pharmaceutical compositions of the formula



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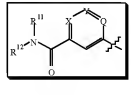
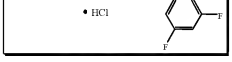


I/I(a)/III, wherein R^1 = -benzamido (right, wherein X = -CH-; Y = -CR^{16}, where R^{16} = -H; Q = CR^{17}, where R^{17} = -H; R^{11} = -propyl; and R^{12} = -propyl); R^2 = -benzyl, optionally disubstituted with halo; R^3 = -H; R^4 = -H; R^5 = -H; R^6 = R^{34}, wherein R^{34} = -H; R^7 = -H; and R^8 = -H, shown to the right, as β-site APP-cleaving enzyme (BACE) inhibitors, useful in the treatment of disorders such as Alzheimer's disease.

Cumming et al. (WO 05/016876) teaches substituted pyrrolidines, hydrochloride salts and pharmaceutical compositions of the formula I/I(a)/III, wherein R^1 = -benzamido (shown above, wherein X = -CH-; Y = -CR^{16}, where R^{16} = -H; Q = CR^{17}, where R^{17} = -H; R^{11} = -propyl; and R^{12} = -propyl); R^2 = -benzyl, optionally disubstituted with fluoro; R^3 = -H; R^4 = -H; R^5 = -H; R^6 = R^{34}, wherein R^{34} = -$(CH_2)_{0-2}$-OR^{32}, wherein R^{32} = C_1-C_{10} alkyl, optionally substituted with -$(CH_2)_{0-3}$-OR^{33}, where R^{33} = -Ph; R^7 = -H; and R^8 = -H, shown to the left above, as β-site APP-cleaving enzyme (BACE-1) inhibitors, useful in the treatment of disorders such as Alzheimer's disease [p. 39, example 1A; HCl salt - p. 17, lines 26-30; also in priority document US 60/493,987 - p. 33, example 2; and pharmaceutical compositions - p. 6, lines 11-13].



Claim Rejections - 35 U.S.C. § 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

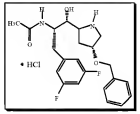
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

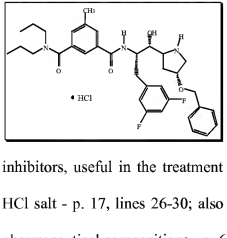
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 2, 8 and 9 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Cumming, et al. in WO 05/016876, in view of McCarty, et al. in *J. Med. Chem.* 13(5), **1970**, pp. 814-819.

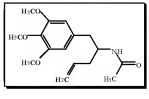
The instant application recites substituted pyrrolidines, hydrochloride salts and pharmaceutical compositions of the formula I/I(a)/III, wherein R_1 = -CH_3 (C_3-C_7cycloalkyl)$_{0-1}$(C_1-C_6alkyl); R^2 = -benzyl; R^3 = -H; R^4 = -H; R^5 = -H; R^6 = R^{34}, wherein R^{34} = -$(CH_2)_{0-2}$-OR^{32}, wherein R^{32} = C_1-C_{10} alkyl, optionally substituted with -$(CH_2)_{0-3}$-OR^{33}, where R^{33} = -Ph; R^7 = -H; and R^8 = -H, shown to the right, as β-site APP-cleaving enzyme (BACE) inhibitors, useful in the treatment of disorders such as Alzheimer's disease.

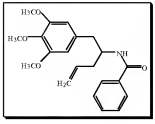


Cumming et al. (WO 05/016876) teaches substituted pyrrolidines, hydrochloride salts and pharmaceutical compositions of the formula I/I(a)/III, wherein R_1 = -Ph; R^2 = -benzyl; R^3 = -H; R^4 = -H; R^5 = -H; R^6 = R^{34}, wherein R^{34} = -$(CH_2)_{0-2}$-OR^{32}, wherein R^{32} = C_1-C_{10} alkyl, optionally substituted with -$(CH_2)_{0-3}$-OR^{33}, where R^{33} = -Ph; R^7 = -H; and R^8 = -H, shown to the left, as β-site APP-cleaving enzyme (BACE-1) inhibitors, useful in the treatment of disorders such as Alzheimer's disease [p. 43, example 3; HCl salt - p. 17, lines 26-30; also in priority document US 60/493,987 - p. 48, example 9; and pharmaceutical compositions - p. 6, lines 11-13].



McCarty et al. (*J. Med. Chem.* 13(5), **1970**) teaches acyclic amides as hypotensive, analgesic and anti-inflammatory agents, wherein synthesis and pharmacological evaluation protocol involved





the routine screening and alternative use of both acyclic benzamides and acetamides. Two representatives of acyclic amides disclosed and evaluated are shown [p. 816, Table 1, -NHCOCH$_3$ - entry 12 (shown right above) and -NHCOPh - entry 21 (shown left)].

The only difference between the instantly recited substituted pyrrolidines, hydrochloride salts and pharmaceutical compositions of the formula I/I(a)/III and Cumming's substituted pyrrolidines, hydrochloride salts and pharmaceutical compositions of the formula I/I(a)/III is the instantly recited substituted pyrrolidines, hydrochloride salts and pharmaceutical compositions of the formula I/I(a)/III have R^1 = -CH$_3$ to provide an acetamide moiety, whereas Cumming's substituted pyrrolidines, hydrochloride salts and pharmaceutical compositions of the formula I/I(a)/III have R^1 = -Ph to provide a benzamide moiety.

The courts have recognized that *rigid application of the "teaching, suggestion, or motivation" test, under which a patent claim is proved obvious only if prior art, nature of problem addressed by inventor, or knowledge of person having ordinary skill in art reveals some motivation or suggestion to combine prior art teachings, is inconsistent with the expansive and flexible "functional approach" to resolution of the obviousness issue, under which: (1) scope and content of prior art are determined; (2) differences between prior art and claims at issue are ascertained; (3) level of ordinary skill in pertinent art is resolved; and (4) secondary considerations such as commercial success, long felt but unsolved needs, and failure of others may be considered, if doing so would prove instructive; therefore, rigid application of the TSM approach was rejected.* (*KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385).

Similarly, the courts have also recognized that *variations of particular work available in*

one field of endeavor may be prompted by design incentives and other market forces, either in the same field or a different one, and if a person of ordinary skill in the art can implement a predictable variation, 35 U.S.C. § 103 likely bars its patentability. (*KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385).

Furthermore, the *fact that a claimed combination of elements was "obvious to try" may be used to show that such a combination was obvious under 35 U.S.C. § 103, since, if there is a design need or market pressure to solve a problem, and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue known options within his or her technical grasp, and if this leads to anticipated success, it is likely the product of ordinary skill and common sense, not innovation.* (*KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385).

The courts recognized that *the narrow conception of the obviousness inquiry, reflected in the rigid application of the "teaching, suggestion, or motivation" test, resulted in erroneous conclusions that the summary judgment of obviousness should be vacated, since decisions were based on: (1) erroneous holdings that courts and patent examiners should look only to problems that a patentee was trying to solve; and (2) erroneous assumption that a person of ordinary skill in the art attempting to solve a problem will be led only to those elements of the prior art designed to solve the same problem.* (*KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385).

We build and create by bringing to the tangible and palpable reality around us new works based on instinct, simple logic, ordinary inferences, extraordinary ideas, and sometimes even genius. These advances, once part of our shared knowledge, define a new threshold from which innovation starts once more. As progress beginning from higher levels of achievement is

expected in the normal course, the results of ordinary innovation are not the subject of exclusive rights under the patent laws. (KSR, 127 S.Ct. at 1746).

Consequently, since: a) Cumming teaches substituted pyrrolidines, hydrochloride salts and pharmaceutical compositions of the formula I/I(a)/III, wherein R_1 = -Ph, to provide a benzamide moiety; b) McCarty teaches the alternative utility of acetamides and benzamides for screening and evaluation as hypotensives, etc., wherein a finite number of identified, predictable solutions (i.e. alkyl amides and aryl amides) are presented and explored; and c) the courts have recognized that a claimed combination of elements would be *obvious to try* and obvious under 35 U.S.C. § 103, if there is a design need or market pressure to solve a problem, and there are a finite number of identified, predictable solutions, one having ordinary skill in the art, at the time this invention was made, would have been motivated to pursue known options within his/her technical grasp and expand on the teachings of both Cumming and McCarty and explore substituted pyrrolidines, hydrochloride salts and pharmaceutical compositions of the formula I/I(a)/III containing acetamides (alkyl amides) as a viable and practical alternative to substituted pyrrolidines, hydrochloride salts and pharmaceutical compositions of the formula I/I(a)/III containing benzamides (aryl amides), with a reasonable expectation of success and similar therapeutic activity, rendering claims 1, 2, 8 and 9 obvious.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Allowable Subject Matter

No claims allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DOUGLAS M. WILLIS, whose telephone number is 571-270-5757. The examiner can normally be reached on Monday thru Thursday from 8:00-6:00 EST. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick Nolan, can be reached on 571-272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/D. M. W./

Examiner, Art Unit 4161

/Patrick J. Nolan/
Supervisory Patent Examiner, Art Unit 4161